

A Retrospective Study of the Teratogenicity of Dermatological Coal Tar Products

Sir,

Medical pix lithantracis (PL) is obtained by fractionated distillation of crude coal tar (CCT). CCT contains at least 10,000 different compounds, including polycyclic aromatic hydrocarbons (PAHs). After dermatological application of PL-containing products, metabolites of PAHs have been found in blood (1) and urine (2). PAHs cause destruction of the oocyte in rodents, both pre-natally (3) and postnatally (4), which leads to decreased fertility. However, there are great differences among species regarding sensitivity to PAHs. The litters from pregnant mice that had been treated with distillates of CCT showed congenital malformations of the urogenital tract in particular, while the litters from pregnant rats mainly presented with characteristic reduced cranial ossification and generalized oedema (5). A search of MEDLINE found no literature regarding the possible foetotoxic effects of CCT-products in humans. Literature regarding the possible teratogenicity of dermatological CCT-products is therefore scarce. This lack of human data led to us to carry out a retrospective pilot study using a questionnaire among women with psoriasis or dermatitis, who had been treated with tar products between 1981 and 1985, when their age varied between 18 and 35 years. This was carried out as a pilot study, because for a representative sample at least 1,000 PL-treated pregnant women are required (for great differentiating power) and it is a retrospective study because a prospective study is not possible for ethical reasons.

RESULTS

In total, 56 out of 64 questionnaires were returned; a response of 88%. The ratio of dermatitis to psoriasis was 1:2, with a mean percentage treated body area of 78% and 90%, respectively. Thirty-one patients (55%) stated that they had no other illness besides their skin disease. The other 25 patients were suffering from 30 disorders, in particular disorders of the locomotor tractus (30%), the immune system (23%) and the respiratory (17%) and endocrine (17%) systems. In addition, complaints of circulatory, gastrointestinal, neurological (epilepsy) and psychiatric (depression) nature were mentioned.

In total, the 56 women had been pregnant 103 times. In 59 out of 103 pregnancies no tar had been used during pregnancy. Of these 59 pregnancies, 11 ended in a spontaneous stillbirth and 45 healthy children and 3 children with a congenital disorder (of the brain, throat and muscles, respectively) were born. So in the group not treated with tar during pregnancy 19% of pregnancies resulted in spontaneous abortion and 5% in a congenital disorder.

In 21 pregnancies, it was uncertain whether or not tar had been used during pregnancy. Of these 21 pregnancies 1 ended in a spontaneous stillbirth and 19 healthy children and 1 child with a congenital heart anomaly were born.

In 23 cases tar was definitely used during pregnancy. Of those pregnancies, 6 ended in a spontaneous abortion and 16 healthy children and 1 child with a lethal congenital anomaly (trisomy 13) were born. Thus, in the tar-treated group 26% of pregnancies resulted in spontaneous abortion and 4% in a congenital disorder.

DISCUSSION

Pregnancies during which the dermatological use of tar was clear were not more troublesome than pregnancies without the dermatological use of tar. However, these data are based on only 23 pregnancies, so they do not allow a general statement regarding the possible teratogenicity of medical coal tar products. In addition, there was no uniformity regarding the time of exposure, and the time of use of tar during the pregnancy varied between the first weeks to after the seventh month. The moment of exposure, however, is essential to make a statement regarding the possible teratogenicity of any product. Starting from the hypothesis that coal tar indeed does have teratogenic effects, these have to be expected after the use of coal tar products during gametogenesis or organogenesis and therefore early in pregnancy at the latest. Patients who come into contact with coal tar late in pregnancy are not at risk and might disguise the possible teratogenicity of dermatological coal tar products. In the event of a further study patients should also be grouped according to time of exposure.

Differences between species might also play a part when the results of this study are compared with the literature on animal experiments. Zangar et al. found similarities and differences in the expressed abnormalities in both species (5). In addition, this study showed that to achieve the same teratogenic effects after dermal exposure to a complex organic mixture, a considerable higher exposure is essential after inhalation compared with oral exposure. In humans this could mean that the dosage of a coal tar product might be of relevance and the main therapeutic dosages of dermatological coal tar might be below the teratogenic dosage. However, extrapolating the dosage of Zangar et al. to humans, the therapeutic dosage exceeds the teratogenic dosage. This might be explained by a difference in sensitivity between species. Another explanation might be the fact that Zangar et al. applied the complex organic mixture to a healthy (relatively thin) animal skin, although in patients PL-containing ointments are applied to diseased skin. Specific induction of certain enzymes also might play a role in explaining these differences.

Remarkably, in the study of Zangar et al. intra-uterine mortality increased in both species, resulting in a dramatic decrease in live births. It is suggested that exposure to coal tar during the phase of organogenesis in pregnancy does cause lethal abnormalities to the foetus. After the use of tar no increased risk of spontaneous abortion was found in our study compared with the same risk in the normal population (20%).

In view of the severity of the findings in *in vitro* and animal studies, caution is appropriate for the present. As long as the data regarding the teratogenicity of dermatological coal tar products are insufficient, it is advised not to prescribe PL in the first trimester of pregnancy and to restrict its use thereafter. Simply deciding not to prescribe PL during the whole of pregnancy excludes the patient from a potential effective therapy of which the harmfulness is predicted on theoretical grounds only.

Further research into the teratogenicity of dermatological

coal tar products is necessary, with a larger patient population, grouping the patients according to time and duration of exposure, the percentage of body area treated, the compliance of the patient regarding the prescribed products, and the use of coal tar products by the fathers. It would also be of value to extend the research with the question as to whether PL-containing products lead to an increase in intrauterine mortality in humans.

REFERENCES

1. Storer JS, DeLeon I, Millikan LE, Laseter JL, Grifing C. Human absorption of crude coal tar products. *Arch Dermatol* 1984; 120: 874–877.
2. Hansen AM, Poulsen OM, Menné T. Longitudinal study of excretion of metabolites of polycyclic aromatic hydrocarbons in urine from two psoriatic patients. *Acta Derm Venereol* 1993; 73: 188–190.
3. Mackenzie KM, Angevine DM. Infertility in mice exposed in utero to benzo(a)pyrene. *Biol Reprod* 1981; 24: 183–191.
4. Mattison DR, Nightingale MS. Oocyte destruction by polycyclic aromatic hydrocarbons is not linked to the inductability of ovarian aryl hydrocarbon hydroxylase activity in backcross mice. *Ped Pharmacol* 1982; 2: 11–21.
5. Zangar RC, Springer DL, Buschbom RL, Mahlum DD. Comparison of fetotoxic effects of a dermally applied complex organic mixture in rats and mice. *Fund Appl Toxicol* 1989; 13: 662–669.

Accepted January 15, 1999.

M.E.J. Franssen¹, G.J. van der Wilt², P.C.M. Pasker de Jong², R.P. Bos³ and W.P. Arnold⁴
Departments of ¹Dermatology, ²Medical Epidemiology, ³Toxicology; University Hospital Nijmegen, PO Box 9101, NL-6500 HB Nijmegen, The Netherlands and ⁴Department of Dermatology, Hospital "Gelderse Vallei", Stationsweg 86, 6711 PV Ede, The Netherlands.
(Correspondence to W. P. Arnold, MD, PhD).

Exfoliative Dermatitis after Long-term Methotrexate Treatment of Severe Psoriasis

Sir,

Severe cutaneous adverse reactions to high-dose methotrexate (MTX) regimens occur occasionally and are rarely misinterpreted. By contrast, low- and intermediate-dose MTX therapy, as frequently used for treatment of severe psoriasis and psoriatic arthropathy, is relatively well tolerated. Skin reactions are rare and when they occur they are often not interpreted as causally related to MTX. Consequently, because of deteriorating skin symptoms that can be interpreted as exacerbating psoriasis, MTX dosage may be increased rather than reduced or discontinued. We present here a case of exfoliative dermatitis following long-term low- to intermediate-dose MTX treatment for severe psoriasis and progressive psoriatic arthropathy.

CASE REPORT

A 37-year-old man with a 7-year history of chronic stationary plaque-type psoriasis had been treated with cignoline, topical and oral corticosteroids, acitretinate and cyclosporin A, as well as with concomitant UVB, photochemotherapy (PUVA) and selective UVB (SUP) radiation because of exacerbated psoriasis and psoriatic arthropathy between 1991 and 1998. Despite intensified treatment and several periods of hospitalization his skin symptoms and arthropathy were progressive. He eventually developed psoriatic erythroderma with pustulosis of his lower legs and generalized arthropathy of the distal and proximal joints. In August 1993, MTX treatment was started at 15 mg per os and subsequently increased to 25 mg weekly. At that time, his weight was 107 kg at a height of 195 cm. In January 1995, he presented with an extremely painful, fluoride arthritis of his fingers and ankle joints. Consecutively, he was administered morphine sulphate (MST[®]) on a regular basis and the MTX treatment was changed to intravenous medication. He also required a wheelchair from this time on.

In February 1998, he again presented with erythroderma, pustulosis of his lower legs and generalized arthropathy under his current intravenous medication with 25 mg MTX per week. Surprisingly, when hospitalized, 12 h after intravenous MTX medication his skin symptoms were severely exacerbated, showing ulcerated psoriatic

plaques and wide areas of exfoliative dermatitis over his whole body. This exacerbation following MTX treatment was observed 3 times. MTX was discontinued and topical treatment with triamcinolone acetone (Volon A[®]) and prednisolone pulse-therapy slowly led to an improvement of skin symptoms. At the same time treatment with mycophenolatemofetil (CellCept[®]) was started, but failed to have a lasting effect even after 5 weeks. The regimen was changed to azathioprin (Imurek[®]), acitretinate (Neotigason[®]) and prednisolone (Decortin H[®]). This led to a stable remission, so that the patient could finally be dismissed into rehabilitation.

DISCUSSION

After 5 years of low- and intermediate-dose MTX treatment, the patient developed acute extensive exfoliative dermatitis and ulcerated psoriatic plaques following intravenous administration of 25 mg MTX. Since psoriatic eruptions under immunosuppressive treatment with 25 mg MTX and topical steroids are extremely unlikely and the skin symptoms gradually improved after cessation of MTX medication, we interpreted his acute illness as MTX-induced skin lesions.

Unfortunately, the patient refused biopsy at that stage. Biopsy is helpful, as skin histology can support the diagnosis of cytotoxic drug-induced changes typically showing single cell necrosis of the epidermis and the acrosyringium.

Several cases of cutaneous adverse reactions of varying clinical patterns, including generalized desquamation, painful erythema and ulceration among others, have been ascribed to high-dose MTX (1–3) or MTX analogues (4, 5). Martins da Cunha et al. (1) described an erythematous skin rash followed by desquamation predominantly localized on the palms and soles after high-dose MTX infusion, but they also pointed out the difficulties in attributing a cutaneous reaction to a particular drug, as patients undergoing chemotherapy often receive many drugs at the same time. We recently observed a similar case of extended exfoliative dermatitis in a 51-year-old male, 10 days after he had received polychemotherapy including high-dose MTX (2.75 g MTX, with subsequent